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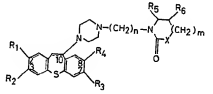
(19)

(54) PIPERAZINYL-DIBENZO [B,F] THIEPINS, METHODS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Genzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to tricyclic compounds. More particularly, the invention is concerned with dibenzo[b,f]thiepin derivatives and a process for the manufacture thereof.

The dibenzo[b,f]thiepin derivatives provided by the present invention are compounds of the general formula



(I)

wherein one of the two symbols R_1 and R_3 or R_3 and R_4 represents a hydrogen atom and the other represents a chlorine or fluorine atom or a methyl, methoxy, methylthio, dimethylsulphamoyl or trifluoromethyl group, n stands for 2 or 3, m stands for zero or 1, X represents a sulphur or oxygen atom or an imino, (lower alkyl)-imino or methylene group and R_5 and R_6 each represent a hydrogen atom or R_5 and R_6 together represent the grouping

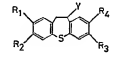
and wherein the bond denoted by a broken line can be hydrogenated, and salts thereof.

As will be evident from the foregoing definition, the compounds of formula I always carry a substituent in each of the aromatic nuclei. One substituent is present in the 2- or 3-position and the other in the 7- or 8-position of the dibenzo[b,f]thiepin moiety. The term "lower alkyl" as used herein means an alkyl group containing from 1 to 7 carbon atoms.

It has been found that the dibenzo[b,f]thiepin derivatives provided by this invention (i.e. the compounds of formula I and their salts) are distinguished by strong central depressant and neuroleptic properties. They can accordingly be used, for example, for the treatment of acute or chronic schizophrenia and also as tranquillizers. Of particular advantage is the fact that no, or only slight, cataleptic side-effects occur so that no, or only insignificant, motoric disorders are observed. A preferred group of dibenzo[b,f]thiepin derivatives provided by the present invention comprises those compounds of formula I in which the bond denoted by a broken line is hydrogenated, and salts thereof. Also preferred are those compounds of formula I in which R_2 and R_3 each represent a hydrogen atom, R_1 represents a methyl group and R_4 represents a chlorine or fluorine atom or a methylthio group, and salts thereof. Those compounds of formula I in which R_2 and R_3 each represent a hydrogen atom, R_1 represents a chlorine atom and R_4 represents a fluorine atom, and salts thereof, are also preferred. Furthermore, those compounds of formula I in which n stands for 2, m stands for zero, X represents an oxygen atom or a methylene group and R_5 and R_6 each represent a hydrogen atom, and salts thereof, are also preferred. Especially preferred dibenzo[b,f]thiepin derivatives of this invention are 1 - [2 - [4 - (8 - chloro - 10,11 - dihydro - 2 - methyl - dibenzo-[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - pyrrolidinone, 3 - [2 - [4 - (8 - fluoro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone, 3 - [2 - [4 - (2 - chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone and 3 - [2 - [4 - (10,11 - dihydro - 2 - methyl - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone, and salts thereof.

According to the process provided by the present invention, the dibenzo[b,f]thiepin derivatives aforesaid are manufactured by

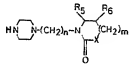
(a) for the manufacture of a compound of formula I in which the bond denoted by a broken line is hydrogenated, reacting a compound of the general formula



(II)

wherein R_1, R_2, R_3 and R_4 have the significance given earlier and Y represents a leaving atom or group,

with a compound of the general formula

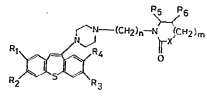


(III)

wherein n, m, X, R_5 and R_6 have the significance given earlier,

or

b) for the manufacture of a compound of formula I in which the bond denoted by a broken line is hydrogenated, reducing an enaminc of the general formula

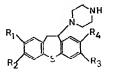


(IV)

wherein R_1, R_2, R_3, R_4, R_5, R_6, n, m and X have the significance given earlier,

or

c) for the manufacture of a compound of formula I in which the bond denoted by a broken line is hydrogenated, reacting a compound of the general formula



(V)

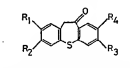
wherein R_1, R_2, R_3 and R_4 have the significance given earlier, with a compound of the general formula

(VI)

wherein Y, n, m, X, R_5 and R_6 have the significance given earlier,

or

d) for the manufacture of a compound of formula I in which the bond denoted by a broken line is not hydrogenated, reacting a compound of the general formula



(VII)

wherein, R_1, R_2, R_3 and R_4 have the significance given earlier, with a compound of formula III hereinbefore, and, if desired, converting the product obtained into a salt.

The leaving atom or group denoted by Y in the starting materials of formula II is preferably a halogen atom or an alkyl-substituted or aryl-substituted sulphonyloxy group. Alkyl or aryl groups present in the leaving group denoted by Y are preferably lower alkyl groups, especially the methyl group, or (C_6—C_{10}) aryl groups, especially the phenyl or p-tolyl group. A halogen atom denoted by Y is preferably a chlorine or bromine atom.

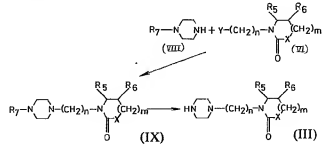
The leaving atom or group denoted by Y in the starting materials of formula II can be introduced, for example, in the following manner:

Y=halogen: A corresponding 10-hydroxy compound is reacted with a suitable halide (e.g. thionyl chloride or thionyl bromide) or with a hydrohalide in the presence of a water-binding agent such as hydrogen chloride and calcium chloride.

Y=alkyl-substituted or aryl-substituted sulphonyloxy: A corresponding 10-hydroxy compound is reacted with an alkyl-substituted or aryl-substituted sulphonic acid halide (e.g. the chloride).

The compounds of general formula II in which Y is a halogen atom or an alkyl substituted or aryl-substituted sulphonyloxy group are described and claimed in our Divisional Application No. 26540/76 (Serial No. 1,464,978).

The starting materials of formula III can be prepared, for example, according to the following formula scheme:



(VIII) (VI) (IX) (III)

In the foregoing formula scheme, Y, n, m, X, R_5 and R_6 have the significance given earlier and R, represents a suitable protecting group; for example, the benzyl group or a lower alkoxycarbonyl group such as the methoxycarbonyl or ethoxycarbonyl group. The condensation of a compound of formula VIII with a compound of formula VI is preferably carried out in the presence of an acid-binding agent (e.g. potassium carbonate or triethylamine). Subsequently, the protecting group is removed from the condensation product of formula IX, the benzyl group being removed by hydrogenolysis and an alkoxycarbonyl group being removed by hydrolysis (e.g. with aqueous alkali).

The preparation of the compounds of formula VI is described hereinafter.

The reaction of a compound of formula II with a compound of formula III can be carried out without the addition of a solvent. If a solvent is used, then this is expediently an organic solvent; for example an aromatic hydrocarbon (e.g. benzene or toluene), a lower alkanol (e.g. methanol or ethanol), a chlorinated hydrocarbon (e.g. methylene chloride, trichloroethylene, chloroform, carbon tetrachloride or chlorobenzene), an aliphatic or cyclic ether (e.g. diethyl ether, tetrahydrofuran or dioxane), dimethylformamide or dimethyl sulphoxide. The reaction is expediently carried out at a temperature between 30° and 200°C, preferably at a temperature in the region of 60°—150°C. The reaction is advantageously carried out in the presence of an acid-binding agent (e.g. an alkali carbonate such as potassium carbonate) or in the presence of an excess of the starting material of formula III.

The reduction of an enamine of formula IV is preferably carried out by treatment with an alkali metal borohydride in the presence of a strong acid. As the alkali metal borohydride there is preferably used sodium or potassium borohydride, particularly sodium borohydride. Lithium borohydride can, however, also be used. The strong acid can be not only an organic acid but also an inorganic acid. The organic acid can be a straight-chain or branched-chain, mono- or dicarboxylic acid containing up to 4 carbon atoms, which may be halo-substituted (e.g. formic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, propionic acid, isobutyric acid and oxalic acid). Acetic acid is preferred and oxalic acid is especially preferred. The inorganic acid can be, in particular, sulphuric acid or a hydrohalic acid, especially hydrochloric acid. A preferred inorganic acid is concentrated sulphuric acid. Since the enamines of formula IV are unstable in the presence of water, the reduction is expediently carried out in the absence of water, there being expediently used only anhydrous acids or only those acids in which, if they contain some water, this is not released (e.g. concentrated sulphuric acid). The reduction with an alkali metal borohydride in the presence of a strong acid is advantageously carried out in an ether such as diethyl ether, tetrahydrofuran, dioxane, diethyleneglycol dimethyl ether (diglyme) or dimethoxyethane and at a temperature between room temperature and the reflux temperature of the mixture. The reduction is preferably carried out under reflux conditions. The reduction of an enamine of formula IV can also be carried out according to other methods; for example, by the treatment with formic acid or zinc and glacial acetic acid. These reduction methods are also preferably carried out at a temperature between room temperature and the reflux temperature of the mixture, preferably at the reflux temperature.

The starting materials of formula V can be prepared, for example, by reacting a compound of formula II with a mono-N-protected piperazine (e.g. N-carbethoxypiperazine). The reaction product is subsequently hydrolysed (e.g. using aqueous alkali). According to another method, a tricylic ketone of formula VII is reacted with a mono-N-protected piperazine (e.g. N-carbethoxypiperazine) essentially in the same manner to that described hereinafter in connection with the reaction of a compound of formula VII with a compound of formula III. The resulting enamine containing a N-protecting group is then reduced at the 10,11-double bond, essentially in the same manner to that described earlier in connection with the reduction of an enamine of formula IV, and subsequently the N-protecting group is hydrolysed off (e.g. using aqueous alkali). The compounds of general formula V are described and claimed in our Divisional Application No. 26541/76 (Serial No. 1,464,979).

The leaving atom or group denoted by Y in the starting materials of formula VI are of the same type as in the starting materials of formula II. The starting materials of formula VI can be prepared, for example, by first converting a compound of the general formula

(X)

wherein m, R_5, R_6 and X have the significance given earlier, into a corresponding alkali metal salt (e.g. the sodium salt). This conversion can be carried out, for example, by treating a compound of formula X with an alkali metal, an alkali metal hydride or an alkali metal amide in an aromatic hydrocarbon (e.g. benzene or toluene) or dimethylformamide. Subsequently, the resulting alkali metal salt is treated with ethylene oxide or propylene oxide and the N-hydroxyethyl or N-hydroxypropyl compound obtained is reacted with a halogenating agent (e.g. thionyl chloride) or with an alkyl-substituted or aryl-substituted sulphonic acid halide (e.g. the chloride) to give a starting material of formula VI.

Starting materials of formula VI in which Y represents a chlorine atom can also be prepared by reacting 1-bromo-2-chloroethane or 1-bromo-3-chloropropane with an aforementioned alkali metal salt of a compound of formula X.

The reaction of a starting material of formula V with a compound of formula VI is expediently carried out in an inert organic solvent; for example in an aromatic hydrocarbon (e.g. benzene or toluene), a chlorinated hydrocarbon (e.g. chloroform), an ether (e.g. dioxane or dimethoxyethane), a lower alkanol (e.g. methanol or ethanol), a ketone (e.g. acetone or methyl ethyl ketone), dimethylformamide or dimethyl sulphoxide. It is preferred to carry out the reaction in the presence of an acid-binding agent such as an alkali metal carbonate (e.g. sodium or potassium carbonate) or an inert organic base (e.g. triethylamine). An excess of the base of formula V can be used and can thus serve as the acid-binding agent. The temperature at which the reaction is carried out preferably lies in the range between room temperature and the boiling point of the reaction mixture.

The reaction of a compound of formula VII with a compound of formula III leads to an enamine of formula I (i.e. a 10,11-unsaturated compound). For example, this reaction is carried out in the presence of a strong acidic agent in an aromatic solvent with heating (e.g. at 80°C to 150°C). As the acidic agent there can be used, for example, a mineral acid such as sulphuric acid or hydrochloric acid or a strong organic acid such as methanesulphonic acid or p-toluenesulphonic acid. As the aromatic solvent there is preferably used benzene, toluene or o-, m- or p-xylene. During the heating there is formed an azeotrope between the solvent and the water formed in the reaction and this can be distilled off. The water formed can also be removed by the addition of a dehydrating agent such as, for example, titanium tetrachloride.

Bases of formula I form salts not only with inorganic acids but also with organic acids; for example, with hydrohalic acids such as hydrochloric acid, hydrobromic acid or hydroiodic acid, with other mineral acids such as sulphuric acid, phosphoric acid or nitric acid, as well as with organic acids such as tartaric acid, citric acid, camphorsulphonic acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, salicylic acid, ascorbic acid, maleic acid or mandelic acid. The preferred salts are the hydrohalides, particularly the hydrochlorides, the maleates and the methanesulphonates. The acid addition salts are preferably prepared in a suitable solvent such as ethanol, acetone or acetonitrile by treatment of the free base with the corresponding, non-aqueous acid. Depending on the molar ratio between the free base and the salt there is obtained, because of the two nitrogen atoms of the piperazine moiety, a salt with one or two mol of acid per mol of base (mono- or di-salts). In the working up of a di-salt there is obtained, depending on the solubility of the mono- or di-salt in the solvent used, the corresponding di- or mono-salt.

The bases of formula I are partly crystalline, solid substances which have relatively good solubility in dimethyl sulphoxide, dimethylformamide, chlorinated hydrocarbons (e.g. chloroform and methylene chloride) or in alkanols (e.g. methanol and ethanol), but which are relatively insoluble in water.

The acid addition salts of the bases of formula I are crystalline, solid substances. They have good solubility in dimethyl sulphoxide, dimethylformamide and alkanols (e.g. methanol and ethanol) and are partly soluble in chloroform, methylene chloride and water. They are relatively insoluble in benzene, diethyl ether and petroleum ether.

A cataleptic action ("wax rigidity", that is abnormally long retention of a forced body position) is considered in central depressant or neuroleptically active compounds to be a disturbing side-effect and produced by motoric disorders. The dibenzo[b,f]thiepin derivatives provided by the present invention have the advantage that they do not possess this disturbing side-effect or only possess it to a very slight extent. For the purpose of demonstration, representative dibenzo[b,f]thiepin derivatives were administered intraperitoneally to rats. The following derivatives were tested:

Derivative A: 1-[2-[4-(8-chloro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl]-2-pyrrolidinone maleate.
Derivative B: 3-[2-[4-(2-chloro-7-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl]-2-oxazolidinone maleate.
Derivative C: 3-[2-[4-(8-fluoro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl]-2-oxazolidinone.
Derivative D: 3-[2-[4-(2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl]-2-oxazolidinone maleate.
Derivative E: 3-[2-[4-(10,11-dihydro-2-methyl-8-methylthio-dibenzo[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl]-2-oxazolidinone maleate.

Chlorpromazine, a well-known central depressant or neuroleptic agent, was used as the standard.

The animals are considered to be cataleptic if the homolateral extremities remain in a crossed position for at least ten seconds. The number of cataleptic animals is noted every 30 minutes for 6 hours. The ED 50 is the dose at which 50% of the animals show catalepsy.

Result:

Derivative	ED 50 mg/kg
A	>100
B	>100
C	75
D	45
E	45
Chlorpromazine	6

The foregoing Table shows that no cataleptic effect or only a slight cataleptic effect occurs in the case of derivatives A—E in contrast to chlorpromazine.

Furthermore, derivatives A—E are considerably less toxic than chlorpromazine, as can be seen from the following figures for the acute toxicity in mice. The figures are based on a duration of action of the derivative of 24 hours.

Derivative	LD 50 mg/kg p.o.
A	3750
B	900
C	1875
D	450
E	3750
Chlorpromazine	200

In order to demonstrate the central depressant or neuroleptic properties of the dibenzo[b,f]thiepin derivatives, representative members were subjected to the following tests:

I. *Rotating rod test*

In the rotating rod test, the ability of mice to carry out a coordinated, motoric performance is tested. After the peroral administration of the test substance, mice are placed on a horizontal, slowly rotating rod and the time is measured until they fall off the rod. The ED 50 is that dose which reduces the retention time by 50% with respect to that before the administration of the test substance.

Result:

Derivative	ED 50 mg. kg
A	7.3
C	2.1
D	1.0
Chlorpromazine	5

Derivatives C and D are clearly superior to chlorpromazine in this test, while derivative A almost approximates chlorpromazine.,

II. *Determination of homovanillic acid*

Rats are injected with the test substance 2 hours before they are killed. Homovanillic acid is extracted from the supernatant of the brain homogenate into butyl acetate and later into an aqueous solution and oxidised with potassium ferricyanide to give a fluorescent dimer. From the increased concentration of homovanillic acid (HVA), it can be determined that the test substance acts like chlorpromazine (i.e. it increases the turnover of dopamine in the basal ganglia). The homovanillic acid titre in untreated rats is arbitrarily fixed at 100%.

Derivative	Dose mg/kg p.o.	Increase of HVA, %
A	50	295
B	50	270
C	50	235
D	45	300
E	50	255
Chlorpromazine	20	320

In this test, derivatives A and B show an activity which almost approaches that of chlorpromazine.

III. *"Pole climbing" test*

The test gives information about behavioural reactions of rats. Rats are trained to avoid, by climbing up a vertical pole in a test chamber, an electrical impulse (unconditioned impulse) released via a wire-latticed floor some seconds after an acoustic signal (conditioned impulse).

The blocking of the conditioned reaction is determined by the parameter ED 50 (mg/kg p.o.); the blocking of the unconditioned reaction is determined by a parameter ED 10 (mg/kg p.o.).

The parameter ED 50 (blocking of the conditioned reaction) gives a measure of the neuroleptic strength of action of the test substance. The quotient ED 10 (blocking of the unconditioned reaction)/ED 50 (blocking of the conditioned reaction) gives a measure of the quality of action of the test substance since, with increasing quotient, a greater selectivity of the neuroleptic action (slighter neurotoxic side-effect) is present.
Result:

Derivative	ED 50 (blocking of the conditioned reaction) mg/kg p.o.	Quotient ED 10 (blocking of the unconditioned reaction). ED 50 (blocking of the conditioned reaction)
C	14	23
D	17	7.6
E	25	12
Chlorpromazine	11.8	2.5

Although the neuroleptic action in C, D and E lies somewhat below that of chlorpromazine, the quality (selectivity) of the neuroleptic action of C, D and E substantially exceeds that of chlorpromazine.

The dibenzo[b,f]thiepin derivatives provided by the present invention can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier. This carrier can be an organic or inorganic, inert carrier material suitable for enteral (e.g. oral) or parenteral administration such as, for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gum arabic, polyalkylene glycols or petroleum jelly. The pharmaceutical preparations can be made up in a solid form (e.g. as tablets, dragées, suppositories or capsules) or in a liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilised and/or may contain adjuvants such as preservatives, stabilisers, wetting agents, emulsifiers, salts for varying the osmotic pressure or buffers. They can also contain other therapeutically valuable materials.

Expedient pharmaceutical dosage forms contain 1 to 200 mg of a compound of formula I or a salt thereof. Expedient oral dosage ranges lie at 0.1 mg/kg per day to 7.5 mg/kg per day. Expedient parenteral dosage ranges lie at 0.01 mg/kg per day to 0.75 mg/kg per day. Moreover, the foregoing ranges can be increased or decreased according to individual requirement and under the directions of a physician.

The following Examples illustrate the process provided by the present invention. References therein to "ether" mean diethyl ether:

Example 1.

11 g of 1-(8-chloro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin-10-yl)-piperazine are heated together with 15.5 g of potassium carbonate, 0.5 g of sodium iodide, 11 g of N-(β-chloroethyl)-pyrrolidinone and 150 ml of toluene for 12 hours under reflux conditions. The mixture is evaporated under reduced pressure. The residue is partitioned between water and ether and the ethereal phase dried over sodium sulphate and evaporated. There is obtained 1-/2-[4-(8-chloro-10,11-dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - pyrrolidinone which melts at 163°—164°C. The maleate melts at 179°—180°C.

The 1-(8-chloro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin-10-yl)-piperazine used as the starting material can be prepared as follows:

426 g of potassium hydroxide are dissolved in water at 50°C and treated with 276 g of 4-chloro-thiophenol. After 15 minutes, 11 g of copper powder and 500 g of 2-iodo-5-methyl-benzoic acid are added and the mixture is subsequently heated under reflux conditions for 7 hours. The mixture is filtered while hot and the filtrate adjusted to a pH-value of 3 at 15°C with concentrated hydrochloric acid and diluted with water. The resulting 2-[(4'-chlorophenyl)-thio]-5-methyl-benzoic

acid is filtered off. The product forms ochre-yellow crystals which melt at 159°—165°C.

583 g of 2-[(4'-chlorophenyl)-thio]-5-methyl-benzoic acid, 3.8 litres of absolute methanol and 250 ml of 96% sulphuric acid are heated under reflux conditions for 24 hours. The mixture is subsequently evaporated under reduced pressure, poured on to ice-cold aqueous sodium bicarbonate solution and extracted with ether. The ether extract is dried over sodium sulphate and evaporated. There is obtained 2-[(4'-chlorophenyl)-thio]-5-methyl-benzoic acid methyl ester as a brown crystallisate.

502 g of 2-[(4'-chlorophenyl)-thio]-5-methyl-benzoic acid methyl ester in 4 litres of absolute tetrahydrofuran are treated dropwise under reflux conditions within 30 minutes with 580 ml of a 70% sodium dihydro-bis(2-methoxy-ethoxy)-aluminate solution in benzene. After stirring for 3 hours, the mixture is cooled to 4°C and treated with 1.5 litres of benzene. The mixture is hydrolysed with 1 litre of 2-N aqueous hydrochloric acid. The precipitate obtained is dissolved by the addition of concentrated hydrochloric acid. The organic phase is washed with water, dried and evaporated. There is obtained 2-[(4'-chlorophenyl)-thio]-5-methyl-benzyl alcohol as a red-brown oil.

446 g of 2-[(4'-chlorophenyl)-thio]-5-methyl-benzyl alcohol in 1 litre of benzene are treated dropwise with 400 g of thionyl chloride and subsequently heated under reflux conditions. The mixture is evaporated under reduced pressure. There is obtained 2-[(4'-chlorophenyl)-thio]-5-methyl-benzyl chloride as a red-brown oil.

480 g of 2-[(4'-chlorophenyl)-thio]-5-methyl-benzyl chloride, 132 g of potassium cyanide, 170 ml of water and 700 ml of ethanol are heated under reflux conditions for 17 hours. The mixture is subsequently concentrated under reduced pressure, diluted with water and extracted with ether. The ether extract is washed with water, dried and evaporated. The crude dark residue is chromatographed with benzene over 1.5 kg of silica dioxide. The purest fractions are concentrated together to about 1 litre, diluted with 1 litre of hexane and crystallised at 0°C. There is obtained 2-[(4'-chlorophenyl)-thio]-5-methyl-phenylacetonitrile as brown crystals which melt at 81°—83°C.

374 g of 2-[(4'-chlorophenyl)-thio]-5-methyl-phenylacetonitrile in 900 ml of ethanol are heated under reflux conditions for 15 hours together with 306 g of potassium hydroxide in 400 ml of water. The mixture is evaporated to dryness under reduced pressure, taken up in water and extracted with ether. The aqueous solution is subsequently treated, under ice-cooling, with 500 ml of concentrated hydrochloric acid and extracted with ether. The ether extract is dried and evaporated. The solid residue is recrystallised from benzene/hexane (2:5). There is obtained 2-[(4'-chlorophenyl)-thio]-5-methyl-phenylacetic acid of melting point 107°—109°C.

286 g of 81—84% polyphosphoric acid are treated at 120°C with 29.2 g of 2-[(4'-chlorophenyl)-thio]-5-methyl-phenylacetic acid and stirred for 15 minutes. The hot solution is poured on to ice/water and extracted with an ether/ethyl acetate mixture. The organic phase is washed successively with water, aqueous sodium bicarbonate solution and aqueous common salt solution, dried and evaporated. There is obtained crude 8-chloro-2-methyl-dibenzo[b,f]thiepin-10(11H)-one which, after recrystallisation from benzene/hexane melts at 123°—129°C.

111.4 g of 8-chloro-2-methyl-dibenzo[b,f]thiepin-10(11H)-one in 1 litre of absolute benzene are treated together with 268 ml of carbethoxypiperazine within 1 hour at 20°—25°C with a solution of 65 ml of titanium tetrachloride in 500 ml of absolute benzene. The mixture is subsequently heated under reflux conditions for 20 hours. The mixture is poured, with strong stirring, into a mixture of 500 ml of saturated, aqueous sodium bicarbonate solution and 700 ml of water, subsequently filtered and rinsed with chloroform. After equilibration of the two phases, the organic phase is dried and evaporated. There is obtained 1-carbethoxy-4-(8-chloro-2-methyl-dibenzo[b,f]thiepin-10-yl)-piperazine as a dark-brown, viscous oil.

41.5 g of 1-carbethoxy-4-(8-chloro-2-methyl-dibenzo[b,f]thiepin-10-yl)-piperazine are treated in 1 litre of absolute diglyme (diethylene glycol dimethyl ether) with 26.5 g of sodium borohydride and stirred for 30 minutes at 25°C. The mixture is then treated dropwise at 20°—30°C within 45 minutes with a solution of 138.6 g of oxalic acid in 800 ml of diglyme. The mixture is now held for 15 hours at 100°C. The whole is evaporated under reduced pressure. The residue is suspended in 1

litre of 2-N aqueous sodium hydroxide and extracted with benzene. The benzene extract is washed with water, dried and evaporated. There is obtained 1-carbethoxy - 4 - (8 - chloro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - piperazine as a red-brown oil whose NMR and IR spectra are in accordance with the structure.

95 g of 1-carbethoxy-4-(8-chloro-10,11-dihydro-2-methyl-dibenzo[b,f]-thiepin-10-yl)-piperazine are stirred together with 1000 ml of ethylene glycol, 77 g of potassium hydroxide and 10 ml of water for 6 hours in a bath of 160°C. The mixture is poured on to ice/water and extracted with ether. The ether extract is washed with water, dried and evaporated. There is obtained 1-(8-chloro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin-10-yl)-piperazine as a red-brown viscous oil. After recrystallisation from acetone/petroleum ether, the product is obtained as crystals which melt at 125°—127°C.

Example 2.

In the same manner as described in Example 1, 3-/2-[4-(8-chloro-10,11-dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone is manufactured from 1-(8-chloro-10,11-dihydro-2-methyl-dibenzo-[b,f]thiepin-10-yl)-piperazine and N-(β-chloroethyl)-oxazolidinone. After recrystallisation from ethyl acetate/petroleum ether, the product melts at 184°—186°C. After recrystallisation from methanol/ether, the maleate melts at 174°—175°C.

Example 3.

19 g of 1-(2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-piperazine together with 15 g of powdered potassium carbonate, 0.3 g of potassium iodide and 150 ml of toluene are treated with 20.4 g of N-(β-chloroethyl)-oxazolidinone and heated under reflux conditions for 20 hours. The mixture is poured on to water and diluted with benzene. The organic phase is washed successively with saturated, aqueous sodium bicarbonate solution and water, dried over magnesium sulphate and evaporated under reduced pressure. The crude 3-/2-[4 - (2 - chloro - 8 - fluoro - 10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-oxazolidinone obtained is converted into the corresponding maleate, which melts at 164°—166°C, by reaction with maleic acid.

The 1-(2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-piperazine used as the starting material can be prepared as follows:

A solution of 214 g of potassium hydroxide in 2 litres of water is treated in a nitrogen atmosphere at 50°C with 122 g of 4-fluoro-thiophenol and stirred for 15 minutes. After the addition of 3.0 g of copper powder and 2.69 g of 5-chloro-2-iodo-benzoic acid, the mixture is heated under reflux conditions for a further 7 hours. The whole is filtered hot and the filtrate acidified with concentrated hydrochloric acid. The precipitate obtained is filtered off, washed to neutrality with water and evaporated under reduced pressure. There is obtained 5-chloro-2-[(4'-fluorophenyl)-thio]-benzoic acid of melting point 176°—177°C.

264 g of 5-chloro-2-[(4'-fluorophenyl)-thiol-benzoic acid in 2 litres of absolute tetrahydrofuran are treated dropwise in a nitrogen atmosphere under reflux conditions with 450 ml of a 70% sodium dihydro-bis(2-methoxy-ethoxy)-aluminate solution in benzene and subsequently boiled under reflux conditions for a further 30 minutes. After cooling to 10°C the mixture is acidified with 1 litre of 3-N hydrochloric acid, then treated with concentrated hydrochloric acid and extracted with ether. The organic phase is washed successively with water, 2-N aqueous sodium hydroxide solution and again with water to a neutral reaction, dried over sodium sulphate, filtered and evaporated. There is obtained 5-chloro-2-[(4'-fluorophenyl)-thio]-benzyl alcohol as a brown oil.

244 g of 5-chloro-2-[(4'-fluorophenyl)-thiol-benzyl alcohol are dissolved in 800 ml of absolute benzene and brought to reflux temperature. This solution is treated dropwise within 40 minutes with 97.5 ml of thionyl chloride and subsequently boiled for a further 30 minutes. The mixture is evaporated under reduced pressure. The residue is treated three times with benzene and evaporated. There is obtained 5-chloro-2-[(4'-fluorophenyl)-thio]-benzyl chloride as a brown oil.

81 g of potassium cyanide in 160 ml of water are treated with 255 g of 5-chloro-2-[(4'-fluorophenyl)-thiol-benzyl chloride in 400 ml of ethanol and heated under reflux conditions for 9 hours. The ethanol is evaporated under reduced pressure, the residue diluted with water and extracted with ether. The ether extract is washed with water, dried over sodium sulphate and evaporated. There is

obtained 5-chloro-2-[(4'-fluorophenyl)-thiol]-phenylacetonitrile as a dark-brown oil.

234 g of 5-chloro-2-[(4'-fluorophenyl)-thiol]-phenylacetonitrile, 500 ml of ethanol, 234 g of potassium hydroxide and 500 ml of water are heated under reflux conditions for 18 hours. The ethanol is evaporated under reduced pressure, the residue dissolved in water and the neutral portions extracted with ether. The aqueous solution is acidified with concentrated hydrochloric acid and extracted with benzene. The benzene phase is washed with water, dried over sodium sulphate, filtered and evaporated under reduced pressure. There is obtained crude 5-chloro-2-[(4'-fluorophenyl)-thiol]-phenylacetic acid as a dark-brown oil. After recrystallisation from benzene/hexane, the product is obtained as crystals which melt at 93°C.

990 g of polyphosphoric acid are heated to 120°C in a nitrogen atmosphere, rapidly treated with 99 g of 5-chloro-2-[(4'-fluorophenyl)-thiol]-phenylacetic acid and stirred for 5 minutes at 120°C. After the addition of ice fragments, the whole is extracted with chloroform. The organic phase is washed successively with water, aqueous sodium hydroxide and water, dried over sodium sulphate and evaporated. There is obtained 2-chloro-8-fluoro-dibenzo[b,f]thiepin-10(11H)-one which melts at 132°C.

60 g of 2-chloro-8-fluoro-dibenzo[b,f]thiepin-10(11H)-one are suspended in 330 ml of ethanol and treated with 13.9 g of sodium borohydride. The mixture is stirred at room temperature for 1 hour, subsequently treated with water and extracted with ether. The organic phase is washed with water, dried over magnesium sulphate and evaporated. There is obtained 2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-ol which melts at 90°C.

58.3 g of 2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-ol, 300 ml of benzene and 21 g of finely powdered calcium chloride are saturated with hydrogen chloride gas at 15°C within 2 hours. The precipitate obtained is filtered off, washed with benzene and evaporated under reduced pressure. There is obtained 2,10-dichloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin as white crystals which melt at 84°—85°C.

24 g of 2,10-dichloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin in 80 ml of chloroform are heated under reflux conditions for 20 hours with 38.4 g of 1-carbethoxypiperazine. The mixture is poured on to ice/water and extracted with chloroform. The organic phase is dried over magnesium sulphate and evaporated under reduced pressure. There is obtained crude, oily 1-carbethoxy-4-(2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-piperazine.

24.5 g of 1-carbethoxy-4-(2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]-thiepin-10-yl)-piperazine, 350 ml of ethylene glycol, 19 g of potassium hydroxide and 1.5 ml of water are heated at 160°C for 1 hour. The mixture is poured on to water and extracted with chloroform. The organic phase is washed with water, dried over magnesium sulphate and evaporated under reduced pressure. There is obtained 1-(2-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-piperazine as a thick oil.

Example 4.

In the same manner as described in Example 3, 3-[2-[4-(2-chloro-7-fluoro-10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone (whose maleate melts, after recrystallisation from ethanol/ether, at 172°—174°C) is manufactured from 1-(2-chloro-7-fluoro-10,11-dihydro - dibenzo[b,f]thiepin-10-yl)-piperazine and N-(β-chloroethyl)-oxazolidinone.

The 1-(2-chloro-7-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-piperazine used as the starting material can be prepared from 5-chloro-2-iodo-benzoic acid and 3-fluoro-thiophenol in the same manner as described in Example 3. There are obtained as intermediates:

5 - Chloro - 2 - [(3' - fluorophenyl) - thiol - benzoic acid; melting point 171°—173°C.
5 - Chloro - 2 - [(3' - fluorophenyl) - thiol - benzyl alcohol; (brown oil).
5 - Chloro - 2 - [(3' - fluorophenyl) - thiol - benzyl chloride; (brown oil).
5 - Chloro - 2 - [(3' - fluorophenyl) - thiol - phenylacetonitrile.
5 - Chloro - 2 - [(3' - fluorophenyl) - thiol - phenylacetic acid; melting point, after recrystallisation from acetone/hexane, 124°—126°C.
2 - Chloro - 7 - fluoro - dibenzo[b,f]thiepin - 10(11H) - one; melting point 117.5°—118.5°C.
2 - Chloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - ol; melting point 98°—99°C.

2,10 - Dichloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin; melting point 119°—120°C.

1 - Carbethoxy - 4 - (2 - chloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]-thiepin - 10 - yl) - piperazine; melting point 117°—118°C.

The 1-(2-chloro-7-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl)-piperazine obtained is present as an oil which can be further processed without further purification.

Example 5.

29 g of 10 - chloro - 8 - fluoro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]-thiepin in 130 ml of chloroform are heated with 45 g of 3-[2-(1-piperazinyl)-ethyl]-2-oxazolidinone under reflux conditions for 20 hours. The chloroform is evaporated, the residue mixed with ether and 1-N sodium hydroxide by stirring and the insoluble base filtered off. The filter cake is washed with water, dried and recrystallised from ethanol. The 3 - [2 - [4 - (8 - fluoro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone thus obtained melts at 174°—175°C.

By reaction of the base with methanesulphonic acid, the dimethane-sulphonate is obtained which, after recrystallisation from ethanol/ether melts at 203°C.

The 10-chloro-8-fluoro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin used as the starting material can be prepared as follows:

A solution of 474.5 g of potassium hydroxide in 3.6 litres of water is treated in a nitrogen atmosphere at 50°C with 217 ml of 4-fluoro-thiophenyl and stirred at room temperature for 15 minutes. After the addition of a few grams of copper powder and of 536 g of 2-iodo-5-methyl-benzoic acid, the mixture is heated under reflux conditions for 7 hours. The mixture is filtered hot, acidified with concentrated hydrochloric acid and filtered again. The residue is washed to neutrality with water and dried under reduced pressure. There is obtained 5-methyl-2-[(4'-fluorophenyl)-thio]-benzoic acid of melting point 166°—167°C.

300 g of 5-methyl-2-[(4'-fluorophenyl)-thio]-benzoic acid in 2 litres of absolute tetrahydrofuran are treated dropwise in a nitrogen atmosphere under reflux conditions with 780 ml of a 70% sodium dihydro-bis(2-methoxy-ethoxy)-aluminate solution in benzene and heated under reflux conditions for a further 1 hour. The mixture is cooled to 4°C, acidified dropwise with 1300 ml of 3-N hydrochloric acid, then treated with concentrated hydrochloric acid and extracted with benzene. The organic phase is successively washed with water, dried over sodium sulphate, filtered and evaporated. There is obtained 5-methyl-2-[(4'-fluorophenyl)thiol-benzyl alcohol as a yellow oil.

337 g of 5-methyl-2-[(4'-fluorophenyl)-thio]-benzyl alcohol are dissolved in 1 litre of absolute benzene and brought to reflux temperature. The solution is treated dropwise with 190 ml of thionyl chloride and boiled for a further 45 minutes. The mixture is evaporated under reduced pressure. The residue is extracted several times with benzene; the benzene extracts are evaporated. There is obtained 5-methyl-2-[(4'-fluorophenyl)-thiol]-benzyl chloride as a brown oil.

115 g of potassium cyanide in 150 ml of water are heated under reflux conditions with 344 g of 5-methyl-2-[(4'-fluorophenyl)-thio]-benzyl chloride in 450 ml of ethanol for 10 hours. The ethanol is subsequently distilled off under reduced pressure. The residue is diluted with water and extracted with benzene. The benzene phase is successively washed with water, dried over sodium sulphate and evaporated. There is obtained 5-methyl-2-[(4'-fluorophenyl)-thiol-phenylaceto-nitrile as a dark-brown oil.

106 g of 5-methyl-2-[(4'-fluorophenyl)-thiol-phenylacetonitrile, 300 ml of ethanol, 100 g of potassium hydroxide and 300 ml of water are heated under reflux conditions for 5 hours. Subsequently, the ethanol is evaporated under reduced pressure. The residue is dissolved in water and the neutral portions extracted with benzene. The aqueous solution is acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate, filtered and evaporated under reduced pressure. There is obtained 5-methyl-2-[(4'-fluorophenyl)-thiol]-phenylacetic acid as a dark-brown oil which, after recrystallisation from benzene/hexane, melts at 117°C.

1810 g of polyphosphoric acid are heated to 128°C in a nitrogen atmosphere, rapidly treated with 173.6 g of 5-methyl-2-[(4'-fluorophenyl)-thiol-phenylacetic acid and stirred for 10 minutes at 120°—130°C. After the addition of ice fragments, the whole is extracted with benzene. The organic phase is washed

successively with water and a saturated, aqueous sodium carbonate solution, dried over sodium sulphate and evaporated. There is obtained 8-fluoro-2-methyl-dibenzo[b,f]thiepin-10(11H)-one which melts at 103°—104°C.

103 g of 8-fluoro-2-methyl-dibenzo[b,f]thiepin-10(11H)-one are suspended in 550 ml of ethanol and treated with 24.3 g of sodium borohydride. The mixture is heated under reflux conditions for about 10 minutes. After the addition of water, the mixture is then extracted with chloroform. The organic phase is successively washed with water, dried over sodium sulphate and evaporated. There is obtained 8-fluoro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin-10-ol as an oil.

103 g of 8-fluoro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin-10-ol, 500 ml of benzene and 38.4 g of finely powdered calcium chloride are saturated at 15°C with hydrogen chloride gas and stirred overnight. The precipitate is filtered off, washed with benzene and evaporated under reduced pressure. There is obtained 10-chloro-8-fluoro-10,11-dihydro-2-methyl-dibenzo[b,f]thiepin which melts at 63°—64°C.

Example 6.

In the same manner as described in Example 5, 3 - [2 - [4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone (which, after recrystallisation from ethyl acetate/petroleum ether, melts at 98°—100°C) is manufactured from 10 - chloro - 10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin and 3 - [2 - (1 - piperazinyl) - ethyl] - 2 oxazolidone. After recrystallisation from ethanol, the dihydrochloride melts at 217°—219°C.

The 10 - chloro - 10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin used as the starting material can be prepared as follows:

150 g of 4-methoxy-anthranilic acid are suspended in 2 litres of water and 80 ml of concentrated hydrochloric acid at 0°C. There is added dropwise thereto with stirring at 0°—5°C within 30 minutes, a solution of 62 g of sodium nitrite in 130 ml of water. The diazonium salt solution thus obtained is stirred at 0°—5°C for a further 15 minutes. Subsequently, a solution of 164 g of potassium iodide in 700 ml of 5-N sulphuric acid is added dropwise at 3°—6°C within 45 minutes. The whole is stirred at room temperature for 30 minutes and subsequently slowly warmed to reflux temperature. After boiling at reflux temperature for 2 hours, the mixture is cooled to room temperature. The brown crystals that separate out are filtered and washed to neutrality with water. The filter cake is dried under reduced pressure. There is obtained 2-iodo-4-methoxy-benzoic acid as brown crystals which melt at 174°C.

411 g of 2-iodo-4-methoxy-benzoic acid, 4 litres of methanol and 400 ml of concentrated sulphuric acid are heated under reflux conditions for 4 hours. The solution is evaporated under reduced pressure, treated with water and extracted with ether. The organic phase is washed successively with aqueous sodium thiosulphate and aqueous sodium bicarbonate and subsequently dried over sodium sulphate. The solution is filtered, evaporated under reduced pressure and distilled. There is obtained 2-iodo-4-methoxy-benzoic acid methyl ester which boils at 95°—98°C/0.04 mm.

205 g of 2-iodo-4-methoxy-benzoic acid methyl ester, 400 ml of methanol, 390 ml of water and 95 g of potassium hydroxide are stirred at 48°C for 30 minutes. The solution is subsequently concentrated under reduced pressure and acidified with aqueous hydrochloric acid. The yellow, crystalline 2-iodo-4-methoxy-benzoic acid obtained is filtered off, washed to neutrality with water and dried. The compound melts at 185°C.

A solution of 170 g of potassium hydroxide in 1.6 litres of water is treated at 50°C in a nitrogen atmosphere with 102 g of 4-methylthio-thiophenol. The whole is subsequently stirred for a further 15 minutes. The mixture is treated with 2.4 g of copper powder and 180 g of 2-iodo-4-methoxy-benzoic acid and heated under reflux conditions for 7 hours. The mixture is filtered hot, acidified with concentrated hydrochloric acid, cooled and filtered. The residue is washed with water and dried under reduced pressure. There is obtained 4-methoxy-2-[(4'-methylthio-phenyl)-thiol-benzoic acid of melting point 202°—293°C.

190 g of 4-methoxy-2-[(4'-methylthio-phenyl)-thiol-benzoic acid in 1.8 litres of absolute tetrahydrofuran are treated dropwise in a nitrogen atmosphere under reflux conditions with 850 ml of a 70% sodium dihydro-bis(2-methoxy-ethoxy)-aluminate solution in benzene. The whole is boiled under reflux conditions for a further 30 minutes. After cooling to 5°C, the mixture is acidified with 500 ml of 3-

N hydrochloric acid and with concentrated hydrochloric acid and extracted with ether. The organic phase is washed successively with water, 2-N aqueous sodium hydroxide solution and again with water and dried over sodium sulphate, filtered and evaporated. There is obtained 4-methoxy-2-[(4'-methylthio-phenyl)-thiol-benzyl alcohol as a brown oil.

165 g of 4-methoxy-2-[(4'-methylthio-phenyl)-thiol-benzyl alcohol are dissolved in 550 ml of absolute benzene and heated under reflux conditions. The solution is treated dropwise within 45 minutes with 62 ml of thionyl chloride and subsequently boiled for a further 30 minutes. The mixture is evaporated under reduced pressure. The residue is extracted three times with benzene. After concentration of the benzene solution, there is obtained 4-methoxy-2-[(4'-methyl-thio-phenyl)-thiol-benzyl chloride as a dark-brown oil.

51 g of potassium cyanide in 110 ml of water are heated with 186 g of 4-methoxy-2-[(4'-methylthio-phenyl)-thiol-benzyl chloride in 270 ml of ethanol under reflux conditions for 9 hours. The ethanol is distilled off under reduced pressure, whereupon the residue is diluted with water and extracted with ether. The ether extracts are washed with water, dried over sodium sulphate and evaporated. There is obtained 4-methoxy-2-[(4'-methylthio-phenyl)-thiol-phenyl-acetonitrile as a dark-brown oil.

160 g of 4-methoxy-2-[(4'-methylthio-phenyl)-thiol-phenylacetonitrile, 330 ml of ethanol, 162 g of potassium hydroxide and 330 ml of water are heated under reflux conditions for 8 hours. Subsequently, the ethanol is evaporated under reduced pressure. The residue is dissolved in about 2 litres of water. The solution is extracted with ether and the ether extract rejected. The aqueous solution is cooled and acidified with concentrated hydrochloric acid. The solution is extracted with benzene and the benzene phase successively washed with water, dried over sodium sulphate, filtered and evaporated. There is obtained crude 4-methoxy-2-[(4'-methylthio-phenyl)-thiol]-phenylacetic acid which, after recrystallisation from benzene/hexane, melts at 125°C.

29.3 g of 4-methoxy-2-l(4'-methylthio-phenyl)-thiol-phenylacetic acid are stirred with 150 g of polyphosphoric acid and 600 ml of toluene under reflux conditions for 17 hours. The mixture is cooled to about 60°C and the toluene solution decanted. The residue is treated with toluene and boiled with stirring. The aqueous residue is treated with ice and water and extracted with toluene. The combined toluene solutions are washed successively with water and aqueous sodium hydroxide solution, dried over sodium sulphate and concentrated under reduced pressure. There is obtained 3-methoxy-8-methylthio-dibenzo[b,f]thiepin-10(11H)-one as a red oil. After recrystallisation from acetone/hexane, the product is obtained as crystals which melt at 127°C.

17.8 g of 3-methoxy-8-methylthio-dibenzo[b,f]thiepin-10(11H)-one are suspended in 150 ml of ethanol and treated with 3.8 g of sodium borohydride. The mixture is stirred for 90 minutes, subsequently treated with water and extracted with ether. The organic phase is washed with water, dried over magnesium sulphate and evaporated. There is obtained 10,11-dihydro-3-methoxy-8-methyl-thio-dibenzo[b,f]thiepin-10-ol of melting point 122°—124°C.

15.7 g of 10,11-dihydro-3-methoxy-8-methylthio-dibenzo[b,f]thiepin-10-ol, 250 ml of benzene and 6 g of finely powdered calcium chloride are saturated at 15°C with 2.5 hours with hydrogen chloride gas and subsequently stirred for a further 3 hours. After the addition of 0.8 g of active carbon, the precipitate is filtered off and washed with benzene. The benzene phase is evaporated under reduced pressure. There is obtained 10-chloro-10,11-dihydro-3-methooxy-8-methylthio-dibenzo[b,f]thiepin; melting point 120°—123°C.

Example 7.

11 g of 1-(10,11-dihydro-3-methoxy-8-methylthio-dibenzo[b,f]thiepin-10-yl)-piperazine are heated together with 15 g of potassium carbonate, 0.5 g of sodium iodide, 11 g of N-(β-chloroethyl)-2-pyrrolidinone and 100 ml of toluene under reflux conditions for 17 hours. The mixture is evaporated under reduced pressure. The residue is partitioned between water and ether and the ethereal phase dried over sodium sulphate and evaporated. The residue obtained is chromatographed with chloroform over aluminium oxide. The 1-/2-[4-(10,11-dihydro-3-methoxy-8-methylthio-dibenzo[b,f]thiepin-10-yl)-1-piperazinyl]ethyl/-2-pyrrolidinone thus obtained is converted into the corresponding dihydrochloride by reaction with hydrogen chloride. The dihydrochloride melts at 202°C.

The 1-(10,11-dihydro-3-methoxy-8-methylthio-dibenzo[b,f]thiepin-10-

yl) - piperazine used as the starting material can be prepared as follows:

24 g of 10-chloro-10,11-dihydro-3-methoxy-8-methylthiodibenzo[b,f]thiepin in 100 ml of chloroform are heated with 55 ml of 1-carbethoxypiperazine under reflux conditions for 20 hours. The mixture is poured on to ice/water and extracted with chloroform. The organic phase is dried over magnesium sulphate and evaporated under reduced pressure. There is obtained crude 1 - carbethoxy - 4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - piperazine.

61 g of 1 - carbethoxy - 4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - piperazine, 600 ml of ethylene glycol, 25 g of potassium hydroxide and 2.7 ml of water are heated at 160°C for 2 hours. The mixture is poured on to water and extracted with benzene. The organic phase is washed with water, dried over magnesium sulphate and evaporated under reduced pressure. There is obtained 1 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - piperazine.

Example 8.

In the same manner as described in Example 5, 3 - [2 - [4 - (8 - chloro - 10,11 - dihydro - 3 - methoxy - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone (which, after recrystallisation from ethyl acetate/petroleum ether, melts at 182°—185°C) is manufactured from 8,10 - dichloro - 10,11 - dihydro - 3 - methoxy - dibenzo[b,f]thiepin and 3 - [2 - (1 - piperazinyl) - ethyl] - 2 - oxazolidinone. After recrystallisation from ethanol/diethyl ether, the dimethanesulphonate melts at 148°—150°C.

The 8,10-dichloro-10,11-dihydro-3-methoxy-dibenzo[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 6 starting from 2-iodo-4-methoxy-benzoic acid and 4-chloro-thiophenol. There are obtained as intermediates:

4-Methoxy-2-[(4-chlorophenyl)-thio]benzoic acid;
melting point 195°—198°C.
4-Methoxy-2-[(4-chlorophenyl)-thio]-benzyl alcohol;
melting point 69°—70°C.
4-Methoxy-2-[(4-chlorophenyl)-thio]-benzyl chloride;
melting point 61°—64°C.
4-Methoxy-2-[(4-chlorophenyl)-thio]-phenylacetonitrile;
(brown oil).
4-Methoxy-2-[(4-chlorophenyl)-thio]-phenylacetic acid;
melting point 117°—118°C.
8-Chloro-3-methoxy-dibenzo[b,f]thiepin-10(11H)-one;
melting point 132°—134°C.
8-Chloro-10,11-dihydro-3-methoxy-dibenzo[b,f]thiepin-10-ol;
melting point 105°—107°C.

The 8,10-dichloro-10,11-dihydro-3-methoxy-dibenzo[b,f]thiepin obtained melts at 100°—102°C.

Example 9.

In the same manner as described in Example 7, 1 - [2 - [4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio-dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 3 - methyl - 2 - imidazolidinone (whose dihydrochloride melts at 191°C) is manufactured from 1 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo-[b,f]thiepin - 10 - yl) - piperazine and 1 - (2 - chloroethyl) - 3 - methyl - 2 - imidazolidinone.

Example 10.

In the same manner as described in Example 7, 1 - [2 - [4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - benzimidazolidinone (whose dihydrochloride melts at 250°C) is manufactured from 1 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - piperazine and N - (2 - chloroethyl) - 2 - benzimidazolidinone.

Example 11.

In the same manner as described in Example 7, 1 - [2 - [4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - piperidinone (whose dihydrochloride melts at 199°C) is manufactured from 1 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - piperazine and N - (2 - chloroethyl) - 2 - piperidinone hydrochloride.

Example 12.

In the same manner as described in Example 7, 3 - [3 - [4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - propyl] - 2 - oxazolidinone (whose dihydrochloride melts at 180°—181°C) is manufactured from 1 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo-[b,f]thiepin - 10 - yl) - piperazine and N - (3 - chloropropyl) - 2 - oxazolidinone.

Example 13.

In the same manner as described in Example 7, 3 - [2 - [4 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - thiazolidinone (whose dihydrochloride melts at 211°—212°C) is manufactured from 1 - (10,11 - dihydro - 3 - methoxy - 8 - methylthio - dibenzo-[b,f]thiepin - 10 - yl) - piperazine and N - (2 - chloroethyl) - 2 - thiazolidinone.

Example 14.

27.4 g of 8-chloro-2-methyl-dibenzo[b,f]thiepin-10(11H)-one, 400 ml of absolute benzene and 40 g of 3-[2-(1-piperazinyl)-ethyl]-2-oxazolidinone are stirred under argon at 20°C. There are added dropwise thereto within 60 minutes, 9.3 ml of titanium tetrachloride in 200 ml of absolute benzene. The mixture is subsequently heated at reflux for 3.5 hours and, after cooling to about 40°C, poured on to a saturated, aqueous sodium bicarbonate solution and stirred for a further 30 minutes. The suspension obtained is filtered and the benzene phase separated. The aqueous phase is back-extracted with 100 ml of benzene. The combined benzene extracts are washed with water, dried over magnesium sulphate, filtered and evaporated. By recrystallisation from acetonitrile, there can be recovered from the residue still unchanged 8-chloro-2-methyl-dibenzo-[b,f]thiepin-10(11H)-one. The mother liquor is evaporated and the residue recrystallised from benzene. There is obtained 3 - [2 - [4 - (8 - chloro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone which melts at 196°—196°C.

Example 15.

1.0 g of 3 - [4 - (8 - chloro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone is stirred at room temperature with 50 ml of diethyleneglycol dimethyl ether (diglyme) and 0.6 g of sodium borohydride for 30 minutes under argon. Thereafter, a solution of 2.8 g of oxalic acid ($C_2H_2O_4.2H_2O$) in 15 ml of diglyme is added dropwise at 20°—30°C. The mixture is stirred at 100°C for 4 hours. The mixture is evaporated under reduced pressure. The residue is taken up in 2-N sodium hydroxide and water and extracted three times with 100 ml of benzene each time. The combined benzene phases are washed with water, dried over magnesium sulphate, filtered and concentrated. The crystalline residue is recrystallised from ethyl acetate/petroleum ether (low boiling). There is obtained 3 - [2 - [4 - (8 - chloro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone of melting point 184°—186°C. The maleate crystallises from methanol/ether and melts at 174°—175°C.

Example 16.

10.6 g of 10-chloro-8-fluoro-10,11-dihydro-3-methyl-dibenzo[b,f]thiepin are heated at reflux together with 200 ml of chloroform and 22.8 g of 3-[2-(1-piperazinyl)-ethyl]-2-oxazolidinone for 30 hours. The mixture is evaporated under reduced pressure. The residue is worked up as described in Example 5. The insoluble base is recrystallised from ethanol. There is obtained 3 - [2 - [4 - (8 - fluoro - 10,11 - dihydro - 3 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone which melts at 173°—175°C. The maleate crystallises from acetone-ether and has a melting point of 147°—149°C.

The 10 - chloro - 8 - fluoro - 10,11 - dihydro - 3 - methyl - dibenzo[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 3 starting from 2-iodo-4-methyl-benzoic acid and 4-fluoro-thiophenol. There are obtained as intermediates:

4-Methyl-2-[(4'-fluorophenyl)-thiol-benzoic acid;
melting point 185°—186°C.
4-Methyl-2-[(4'-fluorophenyl)-thiol-benzyl alcohol;
(orange-coloured oil).
4-Methyl-2-[(4'-fluorophenyl)-thio]-benzyl chloride;
(red-brown oil).

4-Methyl-2-[(4'-fluorophenyl)-thio]-phenylacetonitrile; (brown oil).
4-Methyl-2-[(4'-fluorophenyl)-thio]-phenylacetic acid; melting point 135°—137°C after recrystallisation from acetone/petroleum ether (low boiling).
8-Fluoro-3-methyl-dibenzo[b,f]thiepin-10(11H)-one; melting point 96°—99°C after recrystallisation from ethanol.
8-Fluoro-3-methyl-10,11-dihydro-dibenzo[b,f]thiepin-10-ol; (brown oil).
The 10-chloro-8-fluoro-10,11-dihydro-3-methyl-dibenzo[b,f]thiepin is obtained as a brown oil which crystallises on standing.

Example 17.

In the same manner as described in Example 16, 3 - [2 - [4 - (2 - chloro - 10,11 - dihydro - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazinolidinone (which, after recrystallisation from ethyl acetate/petroleum ether [low boiling], melts at 90°—92°C) is manufactured from 2,10 - dichloro - 10,11 - dihydro - 8 - methylthio - dibenzo[b,f]thiepin and 3 - [2 - (1 - piperazinyl) - ethyl] - 2 - oxazolidinone. The salt formed with 1.8 moles of hydrogen chloride melts at 203°—205°C.
The 2,10 - dichloro - 10,11 - dihydro - 8 - methylthio - dibenzo[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 3 starting from 2-iodo-5-chloro-benzoic acid and 4-methylthio-thiophenol. There are obtained as intermediates:
5-Chloro-2-[(4'-methylthio-phenyl)thio]-benzoic acid; melting point 170°—180°C.
5-Chloro-2-[(4'-methylthio-phenyl)thio]-benzyl alcohol; (red-brown oil).
5-Chloro-2-[(4'-methylthio-phenyl)thio]-benzyl chloride; (red-brown oil).
5-Chloro-2-[(4'-methylthio-phenyl)thio]-phenylacetonitrile; (dark, red-brown oil).
5-Chloro-2-[(4'-methylthio-phenyl)thio]-phenylacetic acid; melting point 112°—113°C after recrystallisation from ethyl acetate/petroleum ether (low boiling).
2-Chloro-8-methylthio-dibenzo[b,f]thiepin-10(11H)-one; melting point 173°—175°C after recrystallisation from xylene.
2-Chloro-10,11-dihydro-8-methylthio-dibenzo[b,f]thiepin-10-ol; (yellow crystals).
The 2,10 - dichloro - 10,11 - dihydro - 8 - methylthio - dibenzo[b,f]thiepin is obtained as a crude oil which can be employed in the reaction mentioned earlier without further purification.

Example 18.

In the same manner as described in Example 16, 3 - [2 - [4 - (10,11 - dihydro - 3 - methyl - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone (which, after recrystallisation from ethanol, melts at 140°—143°C) is manufactured from 10 - chloro - 10,11 - dihydro - 3 - methyl - 8 - methylthio - dibenzo[b,f]thiepin and 3 - [2 - (1 - piperazinyl) - ethyl] - 2 - oxazolidinone. The maleate crystallises from acetone/ether and melts at 151°—153°C.
The 10 - chloro - 10,11 - dihydro - 3 - methyl - 8 - methylthio - dibenzo[b,f]-thiepin used as the starting material can be prepared in the same manner as described in Example 3 starting from 2-iodo-4-methyl-benzoic acid and 4-methyl-thio-thiophenol. There are obtained as intermediates:
4-Methyl-2-[(4'-methylthio-phenyl)thio]-benzoic acid; melting point 250°—255°C.
4-Methyl-2-[(4'-methylthio-phenyl)thio]-benzyl alcohol; (yellow oil which crystallises on standing).
4-Methyl-2-[(4'-methylthio-phenyl)thio]-benzyl chloride; (brown oil).
4-Methyl-2-[(4'-methylthio-phenyl)thio]-phenylacetonitrile; (brown oil).
4-Methyl-2-[(4'-methylthio-phenyl)thio]-phenylacetic acid; melting point 140°—142°C after recrystallisation from acetone/petroleum ether (low boiling).

3-Methyl-8-methylthio-dibenzo[b,f]thiepin-10(11H)-one;
melting point 108°—114°C after recrystallisation from ethanol.
10,11-Dihydro-3-methyl-8-methylthio-dibenzo[b,f]thiepin-10-ol;
(red-brown oil).

The 10 - chloro - 10,11 - dihydro - 3 - methyl - 8 - methylthio - dibenzo[b,f]-thiepin is obtained as a yellow crystalline mass which can be employed in the reaction mentioned earlier without further purification.

Example 19.

In the same manner as described in Example 16, 3 - [2 - [4 - (10,11 - dihydro - 2 - methyl - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone (which, after recrystallisation from ethyl acetate/petroleum ether [low boiling], melts at 122°—123°C) is manufactured from 10 - chloro - 10,11 - dihydro - 2 - methyl - 8 - methylthio - dibenzo[b,f]thiepin and 3 - [2 - (1 - piperazinyl) - ethyl] - 2 - oxazolidinone. The maleate crystallises from acetone/ether and melts at 156°—158°C. The dimethanesulphonate crystallises from methanol/ether and melts at 211°—213°C (the compound contains 1.54% water).

The 10 - chloro - 10,11 - dihydro - 2 - methyl - 8 - methylthio - dibenzo-[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 3 starting from 2-iodo-5-methyl-benzoic acid and 4-methyl-thio-thiophenol. There are obtained as intermediates:

5-Methyl-2-[(4'-methylthio-phenyl)thio]-benzoic acid;
melting point 153°—157°C.
5-Methyl-2-[(4'-methylthio-phenyl)thio]-benzyl alcohol;
(yellow oil which crystallises on standing).
5-Methyl-2-[(4'-methylthio-phenyl)thio]-benzyl chloride;
(brown oil).
5-Methyl-2-[(4'-methylthio-phenyl)thio]-phenylacetonitrile;
(red oil).
5-Methyl-2-[(4'-methylthio-phenyl)thio]-phenylacetic acid;
melting point 89°—92°C after recrystallisation from ethyl acetate/petroleum ether (low boiling).
2-Methyl-8-methylthio-dibenzo[b,f]thiepin-10(11H)-one;
melting point 109°—111°C after recrystallisation from ethanol.
10,11-Dihydro-2-methyl-8-methylthio-dibenzo[b,f]thiepin-10-ol;
(red oil).

The 10 - chloro - 10,11 - dihydro - 2 - methyl - 8 - methylthio - dibenzo[b,f]-thiepin is obtained as a crude, crystalline mass which can be employed in the reaction mentioned earlier without further purification.

Example 20.

25 g of 1 - (3 - chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - piperazine are stirred with 25.6 g of N-(2-chloroethyl)-oxazolidinone, 20 g of potassium carbonate, 0.4 g of sodium iodide and 200 ml of toluene at boiling temperature for 5 hours. The mixture is cooled, treated with water and extracted with benzene. The benzene solution is washed with sodium bicarbonate and with water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 3 - [2 - [4 - (3 - chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - oxazolidinone as a brown oil which is dissolved in ethanol and treated with an ethanolic maleic acid solution. By cooling and treatment with acetone and ether, there is obtained 3 - [2 - [4 - (3 - chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - oxazolidinone maleate which melts at 143°—146°C.

The 1 - (3 - chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - piperazine used as the starting material can be prepared in the same manner as described in Example 3 starting from 4-chloro-2-iodo-benzoic acid and 4-fluoro-thiophenol. There are obtained as intermediates:

4-Chloro-2-[(4'-fluorophenyl)-thio]-benzoic acid;
melting point 212°—214°C.
4-Chloro-2-[(4'-fluorophenyl)-thio]-benzyl alcohol;
melting point 86°—87°C.
4-Chloro-2-[(4'-fluorophenyl)-thio]-benzyl chloride;
(brown oil).
4-Chloro-2-[(4'-fluorophenyl)-thio]-phenylacetonitrile;
(black oil).

4-Chloro-2-[(4'-fluorophenyl)-thio]-phenylacetic acid; melting point 97°—100°C.
3-Chloro-8-fluoro-dibenzo[b,f]thiepin-10(11H)-one; melting point 160°—161°C.
3-Chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-ol; melting point 113°—115°C.
3,10-Dichloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin; melting point 133°—134.5°C.
1-Carbethoxy-4-[3-chloro-8-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-yl]-piperazine; (yellow oil).

The 1 - (3 - chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - piperazine is obtained as a brown oil which can be employed in the reaction mentioned earlier without further purification.

Example 21.

15.4 g of 10 - chloro - 8 - fluoro - 10,11 - dihydro - 3 - methoxy - dibenzo-[b,f]thiepin are treated with 41 g of 3 - [2 - (1 - piperazinyl) - ethyl] - 2 - oxazolidinone and stirred at 120°—130°C (internal temperature) for 10 minutes. The cooled mixture is treated with 2-N sodium hydroxide and extracted with chloroform. The chloroform solution is washed to neutrality with water and shaken out with dilute methanesulphonic acid. The acid solution is made alkaline with sodium hydroxide and the base extracted with chloroform. The organic solution is washed with water, dried over magnesium sulphate and concentrated. The residue is recrystallised from acetone. There is obtained 3 - [2 - [4 - (8 - fluoro - 10,11 - dihydro - 3 - methoxy - dibenzo[b,f]thiepin - 10 - yl) - piperazinyl] - ethyl] - 2 - oxazolidinone of melting point 177°—179°C. The corresponding maleate melts at 212°—214°C.

The 10 - chloro - 8 - fluoro - 10,11 - dihydro - 3 - methoxy - dibenzo[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 3. There are obtained as intermediates:
4-Methoxy-2-[(4'-fluorophenyl)-thio]-benzoic acid; melting point 200°—202°C.
4-Methoxy-2-[(4'-fluorophenyl)-thio]-benzyl alcohol; (yellow oil).
4-Methoxy-2-[(4'-fluorophenyl)-thio]-benzyl chloride; (brown oil).
4-Methoxy-2-[(4'-fluorophenyl)-thio]-phenylacetonitrile; (brown oil).
4-Methoxy-2-[(4'-fluorophenyl)-thio]-phenylacetic acid; melting point 78°—81°C.
8-Fluoro-3-methoxy-dibenzo[b,f]thiepin-10(11H)-one; melting point 112°—114°C.
8-Fluoro-10,11-dihydro-3-methoxy-dibenzo[b,f]thiepin-10-ol; (yellow oil).

The 10 - chloro - 8 - fluoro - 10,11 - dihydro - 3 - methoxy - dibenzo[b,f]thiepin obtained melts at 74°—76°C.

Example 22.

17 g of 3,10 - dichloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin are treated with 45.5 g of 3-[2-(1-piperazinyl)-ethyl]-2-oxazolidinone and stirred at 120°—130°C (internal temperature) for 8 minutes. The mixture is treated with 2-N sodium hydroxide and extracted with ether. The ether solution is washed to neutrality and shaken out with dilute methanesulphonic acid. The acid solution is made alkaline with sodium hydroxide and extracted with methylene chloride. The organic solution is washed with water and dried over magnesium sulphate. The residue is recrystallised from acetone. There is obtained 3-[2-[4-(3-chloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone (melting point 168°—170°C) which is converted into the dimethanesulphonate (melting point 191°—193°C) by reaction with methanesulphonic acid.

The 3,10 - dichloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 3 starting from 4-chloro-2-iodo-benzoic acid and 3-fluoro-thiophenol. There are obtained as intermediates:
4-Chloro-2-[(3'-fluorophenyl)-thio]-benzoic acid; melting point 183°—185°C.

4-Chloro-2-[(3'-fluorophenyl)-thio]-benzyl alcohol; (oil).
4-Chloro-2-[(3'-fluorophenyl)-thio]-benzyl chloride; (oil).
4-Chloro-2-[(3'-fluorophenyl)-thio]-phenylacetonitrile; (oil).
4-Chloro-2-[(3'-fluorophenyl)-thio]-phenylacetic acid; melting point 117°—119°C.
3-Chloro-7-fluoro-dibenzo[b,f]thiepin-10(11H)-one; melting point 145°—148°C.
3-Chloro-7-fluoro-10,11-dihydro-dibenzo[b,f]thiepin-10-ol; melting point 103°—105°C.

The 3,10 - dichloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin obtained melts at 117°—118°C.

Example 23.

11.6 g of 10 - chloro - 8 - fluoro - 10,11 - dihydro - 3 - trifluoro - methyl - dibenzo[b,f]thiepin are treated with 27.8 g of 3-[2-(1-piperazinyl)-ethyl]-2-oxazolidinone and stirred at 115°—120°C for 10 minutes. The mixture is cooled and treated with 2-N sodium hydroxide. The product separating as an oil is extracted with ether, the organic solution washed to neutrality with water and shaken out with a dilute, aqueous methanesulphonic acid solution. The aqueous solution is made alkaline with sodium hydroxide and extracted with ether. The ether solution is washed with water, dried over magnesium sulphate and concentrated. There is obtained 3 - /2 - [4 - (8 - fluoro - 10,11 - dihydro - 3 - trifluoromethyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone as a yellow oil which is converted into the dimethanesulphonate (melting point 149°—151°C) by the addition of methanesulphonic acid.

The 10 - chloro - 8 - fluoro - 10,11 - dihydro - 3 - trifluoromethyl - dibenzo-[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 3 starting from 2-iodo-4-trifluoromethyl-benzoic acid and 4-fluoro-thiophenol. There are obtained as intermediates:

2-[(4'-Fluorophenyl)-thio]-4-trifluoromethyl-benzoic acid; melting point 161°—163°C.
2-[(4'-Fluorophenyl)-thio]-4-trifluoromethyl-benzyl alcohol; boiling point $_{0,3\ mmHg}$: 108°—125°C; melting point 53.5°—55°C.
2-[(4'-Fluorophenyl)-thio]-4-trifluoromethyl-benzyl chloride; (oil).
2-[(4'-Fluorophenyl)-thio]-4-trifluoromethyl-phenylacetonitrile; melting point $_{0,3\ mmHg}$: 114°—120°C.
2-[(4'-Fluorophenyl)-thio]-4-trifluoromethyl-phenylacetic acid; melting point 117°—119°C.
8-Fluoro-3-trifluoromethyl-dibenzo[b,f]thiepin-10(11H)-one; melting point 88°—89°C.
8-Fluoro-10,11-dihydro-3-trifluoromethyl-dibenzo[b,f]thiepin-10-ol; (yellow oil).

The 10 - chloro - 8 - fluoro - 10,11 - dihydro - 3 - trifluoromethyl - dibenzo-[b,f]thiepin obtained melts at 73°—75°C.

Example 24.

20 g of 2,10 - dichloro - 10,11 - dihydro - 7 - methyl - dibenzo[b,f]thiepin are stirred with 41 g of 3-[2-(1-piperazinyl)-ethyl]-2-oxazolidinone and 400 ml of chloroform at boiling temperature for 20 hours. The solution is cooled and washed successively with 2-N sodium hydroxide and with water. The organic phase is decanted off and extracted with dilute methanesulphonic acid. The acid solution is made alkaline with sodium hydroxide and the oil which separates out is shaken out with ether. The ether solution is washed with water, dried over magnesium sulphate and evaporated under reduced pressure. There is obtained 3 - /2 - [4 - (2 - chloro - 10,11 - dihydro - 7 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone (melting point 161°—163°C) which is converted into the corresponding dimethanesulphonate (melting point 187°—189°C) by reaction with methanesulphonic acid.

The 2,10 - dichloro - 10,11 - dihydro - 7 - methyl - dibenzo[b,f]thiepin used as the starting material can be prepared in the same manner as described in Example 3 starting from 5-chloro-2-iodo-benzoic acid and 3-methyl-thiophenol.

There are obtained as intermediates:
5-Chloro-2-[(3'-methyl-phenyl)-thio]-benzoic acid; melting point 163°—166°C.
5-Chloro-2-[(3'-methyl-phenyl)-thio]-benzyl chloride; (brown oil).
5-Chloro-2-[(3'-methyl-phenyl)-thio]-phenylacetonitrile; (brown oil).
5-Chloro-2-[(3'-methyl-phenyl)-thio]-phenylacetic acid; melting point 112°—114°C.
2-Chloro-7-methyl-dibenzo[b,f]thiepin-10(11H)-one; melting point 113°—115°C.
2-Chloro-10,11-dihydro-7-methyl-dibenzo[b,f]thiepin-10-ol; melting point 136°—138°C.
The 2,10 - dichloro - 10,11 - dihydro - 7 - methyl - dibenzo[b,f]thiepin obtained melts at 145°—147°C.

The following Examples illustrate pharmaceutical preparations containing the dibenzo[b,f]thiepin derivatives provided by the present invention:

Example A.

Tablets	Per tablet
3-/2-[4-(8-Fluoro-10,11-dihydro-2-methyl-dibenzo-[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-oxazolidinone	100 mg
Lactose	202 mg
Maize starch	80 mg
Hydrolysed maize starch	20 mg
Calcium stearate	8 mg
Total weight	410 mg

The active ingredient, lactose, maize starch and hydrolysed maize starch are mixed together and granulated with water to a viscous paste. This paste is passed through a sieve and subsequently dried overnight at 45°C. The dried granulate is passed through a sieve and subsequently mixed with the calcium stearate. The mixture obtained is pressed to tablets of weight 410 mg and about 10 mm diameter.

Example B.

Tablets	Per tablet
3-/2-[4-(8-Fluoro-10,11-dihydro-2-methyl-dibenzo-[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-oxazolidinone	25.0 mg
Lactose	114.0 mg
Maize starch	50.0 mg
Gelatinised maize starch	8.0 mg
Calcium stearate	3.0 mg
Total weight	200.0 mg

The active ingredient, lactose, maize starch and gelatinised maize starch are mixed intimately with one another. The mixture is passed through a comminuting machine and subsequently moistened with water to give a thick paste. The moist mass is passed through a sieve. The moist granulate is dried at 45°C. The dried granulate is mixed thoroughly with the calcium stearate. The granulate is now pressed to tablets of weight 200 mg and about 8 mm diameter.

Example C.

Tablets	Per tablet
3-/2-[4-(8-Fluoro-10,11-dihydro-2-methyl-dibenzo-[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-oxazolidinone dimethanesulphonate	14.5 mg
Lactose	124.5 mg
Maize starch	50.0 mg
Gelatinised maize starch	8.0 mg
Calcium stearate	3.0 mg
Total weight	200.0 mg

The active ingredient, lactose, maize starch and gelatinised maize starch are mixed intimately with one another. The mixture is passed through a comminuting machine and subsequently moistened with water to give a thick paste. The moist mass is passed through a sieve. The moist granulate is dried at 45°C. The dried granulate is mixed thoroughly with the calcium stearate. The granulate is now pressed to tablets of weight 200 mg and about 8 mm diameter.

Example D.

Tablets	Per tablet
1-/2-[4-(8-Chloro-10,11-dihydro-2-methyl-dibenzo-[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-pyrrolidinone maleate	25.00 g
Lactose	110 g
Maize starch	61.00 g
Talc	3.40 g
Magnesium stearate	0.60 g
Total weight	200.00 g

The ingredients are mixed intimately with one another and pressed to tablets each of 200 mg. Subsequently, they are coated with ethyl cellulose and Carbowax (trade mark).

Example E.

Capsules	Per capsule
3-/2-[4-(8-Fluoro-10,11-dihydro-2-methyl-dibenzo-e[bf]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-oxazolidinone dimethanesulphonate	29.0 mg
Lactose	156.0 mg
Maize starch	30.0 mg
Talc	5.0 mg
Total weight	220.0 mg

The active ingredient, lactose and maize starch are mixed intimately with one another and passed through a comminuting machine. The mixture is now mixed thoroughly with the talc and filled into hard gelatine capsules.

Example F.

Capsules	Per capsule
3-/2-[4-(8-Fluoro-10,11-dihydro-2-methyl-dibenzo-[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-oxazolidinone	25.5 mg
Lactose	159.5 mg
Maize starch	30.0 mg
Talc	5.0 mg
Total weight	220.0 mg

The active ingredient, lactose and maize starch are mixed intimately with one another and passed through a comminuting machine. The mixture is now mixed thoroughly with the talc and filled into hard gelatine capsules.

Example G.

Parenteral preparation	
Each 1 ml ampoule contains:	
3-/2-[4-(8-Fluoro-10,11-dihydro-2-methyl-dibenzo-[b,f]thiepin-10-yl)-1-piperazinyl]-ethyl/-2-oxazolidinone	10.20 mg (2% excess)
Methanesulphonic acid for injection	2.22 mg
Glucose for injection	40.0 mg
Water for injection q.s. ad	1 ml

In a glass vessel there are dissolved in 8000 ml of water for injection with stirring at room temperature, successively:

22.2 g of methanesulphonic acid for injection,
102 g of active ingredient and
400 g of glucose.

Subsequently, water for injection is added to a total volume of 10,000 ml. The solution is either aseptically filtered, filled into colourless ampoules, gassed with nitrogen and sealed or filled into colourless ampoules, gassed with nitrogen, sealed and subsequently sterilised in a current of steam or autoclaved at 120°C for 30 minutes.

Instead of the active ingredients used in Examples A—G, there can of course also be used in the preparations described therein, other dibenzo[b,f]thiepin derivatives provided by the present invention, for example:

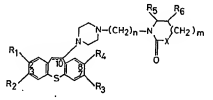
3 -/2 - [4 - (2 - Chloro - 7 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone or the maleate thereof.

3 - / - 2 - [4 - (2 - Chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 oxazolidinone or the maleate thereof.

3 - /2 - [4 - (10,11 - Dihydro - 2 - methyl - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone or the maleate thereof.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



(I)

wherein one of the two symbols R_1 and R_2 or R_3 and R_4 represents a hydrogen atom and the other represents a chlorine or fluorine atom or a methyl, methoxy, methylthio, dimethylsulphamoyl or trifluoromethyl group, n stands for 2 or 3, m stands for zero or 1, X represents a sulphur or oxygen atom or an imino, (lower alkyl)-imino or methylene group and R_5 and R_6 each represent a hydrogen atom or R_5 and R_6 together represent the grouping

and wherein the bond denoted by a broken line can be hydrogenated, and salts thereof.

2. Dibenzo[b,f]thiepin derivatives according to claim 1, wherein the bond denoted by a broken line is hydrogenated.

3. Dibenzo[b,f]thiepin derivatives according to claim 1 or claim 2, wherein R_2 and R_3 each represent a hydrogen atom, R_1 represents a methyl group and R_4 represents a chlorine atom.

4. Dibenzo[b,f]thiepin derivatives according to claim 1 or claim 2, wherein R_2 and R_3 each represent a hydrogen atom, R_1 represents a methyl group and R_4 represents a fluorine atom.

5. Dibenzo[b,f]thiepin derivatives according to claim 1 or claim 2, wherein R_2 and R_3 each represent a hydrogen atom, R_1 represents a methyl group and R_4 represents a methylthio group.

6. Dibenzo[b,f]thiepin derivatives according to claim 1 or claim 2, wherein R_2 and R_3 each represent a hydrogen atom, R_1 represents a chlorine atom and R_4 represents a fluorine atom.

7. Dibenzo[b,f]thiepin derivatives according to any one of the claims 1 to 6 inclusive, wherein n stands for 2, m stands for zero, X represents an oxygen atom or a methylene group and R_5 and R_6 each represent a hydrogen atom.

8. 1 - /2 - [4 - (8 - Chloro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - pyrrolidinone and salts thereof.

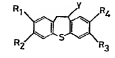
9. 3 - /2 - [4 - (8 - Fluoro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone and salts thereof.

10. 3 - /2 - [4 - (2 - Chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone and salts thereof.

11. 3 - /2 - [4 - (10,11 - Dihydro - 2 - methyl - 8 - methylthio - dibenzo[b,f]-thiepin - 10 - yl) - 1 - piperazinyl] - ethyl/ - 2 - oxazolidinone and salts thereof.

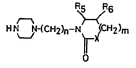
12. A process for the manufacture of the dibenzo[b,f]thiepin derivatives claimed in claim 1, which process comprises

(a) for the manufacture of a compound of formula I in which the bond denoted by a broken line is hydrogenated, reacting a compound of the general formula



(II)

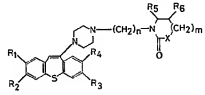
wherein R_1, R_2, R_3 and R_4 have the significance given in claim 1 and Y represents a leaving atom or group,
with a compound of the general formula



(III)

wherein n, m, X, R_5 and R_6 have the significance given in claim 1,
or

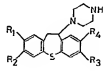
b) for the manufacture of a compound of formula I in which the bond denoted by a broken line is hydrogenated, reducing an enamine of the general formula



(IV)

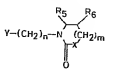
wherein R_1, R_2, R_3, R_4, R_5, R_6, n, m and X have the significance given in claim 1,
or

c) for the manufacture of a compound of formula I in which the bond denoted by a broken line is hydrogenated, reacting a compound of the general formula



(V)

wherein R_1, R_2, R_3 and R_4 have the significance given in claim 1,
with a compound of the general formula

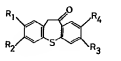


(VI)

wherein n, m, X, R_5 and R_6 have the significance given in claim 1 and Y has the significance given earlier in this claim,

or

d) for the manufacture of a compound of formula I in which the bond denoted by a broken line is not hydrogenated, reacting a compound of the general formula



(VII)

wherein R_1, R_2, R_3 and R_4 have the significance given in claim 1, with a compound of formula III given earlier in this claim, and, if desired, converting the product obtained from any of methods (a) to (d) into a salt.

13. A process according to claim 12 for the manufacture of the dibenzo[b,f]-thiepin derivatives claimed in claim 2, wherein a compound of formula II is reacted with a compound of formula III or an enamine of formula IV is reduced or a compound of formula V is reacted with a compound of formula VI.

14. A process according to claim 12 or claim 13 for the manufacture of the dibenzo[b,f]thiepin derivatives claimed in claim 3, wherein there is used a starting material of formula II, IV, V or VII in which R_1, R_2, R_3 and R_4 have the significance given in claim 3.

15. A process according to claim 12 or claim 13 for the manufacture of the dibenzo[b,f]thiepin derivatives claimed in claim 4, wherein there is used a starting material of formula II, IV, V or VII in which R_1, R_2, R_3 and R_4 have the significance given in claim 4.

16. A process according to claim 12 or claim 13 for the manufacture of the dibenzo[b,f]thiepin derivatives claimed in claim 5, wherein there is used a starting material of formula II, IV, V or VII in which R_1, R_2, R_3 and R_4 have the significance given in claim 5.

17. A process according to claim 12 or claim 13 for the manufacture of the dibenzo[b,f]thiepin derivatives claimed in claim 6, wherein there is used a starting material of formula II, IV, V or VII in which R_1, R_2, R_3 and R_4 have the significance given in claim 6.

18. A process according to any one of claims 12 to 17 inclusive for the manufacture of the dibenzo[b,f]thiepin derivatives claimed in claim 7, wherein there is used a starting material of formula III, IV or VI in which n, m, X, R_5 and R_6 have the significance given in claim 7.

19. A process according to claim 12 for the manufacture of 1 - [2 - [4 - (8 - chloro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - pyrrolidinone and of salts thereof, wherein there are used starting materials of formulae II and III, formula IV or formulae V and VI in which R_1 represents a methyl group, R_2, R_3, R_5 and R_6 each represent a hydrogen atom, R_4 represents a chlorine atom, n stands for 2, m stands for zero and X represents a methylene group.

20. A process according to claim 12 for the manufacture of 3 - [2 - [4 - (8 - fluoro - 10,11 - dihydro - 2 - methyl - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone and salts thereof, wherein there are used starting materials of formulae II and III, formula IV or formulae V and VI in which R_1 represents a methyl group, R_2, R_3, R_5 and R_6 each represent a hydrogen atom, R_4 represents a fluorine atom, n stands for 2, m stands for zero and X represents an oxygen atom.

21. A process according to claim 12 for the manufacture of 3 - [2 - [4 - (2 - chloro - 8 - fluoro - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone and of salts thereof, wherein there are used starting materials of formulae II and III, formula IV or formulae V and VI in which R_1 represents a chlorine atom, R_2, R_3, R_5 and R_6 each represent a hydrogen atom, R_4 represents a fluorine atom, n stands for 2, m stands for zero and X represents an oxygen atom.

22. A process according to claim 12 for the manufacture of 3 - [2 - [4 - (10,11 - dihydro - 2 - methyl - 8 - methylthio - dibenzo[b,f]thiepin - 10 - yl) - 1 - piperazinyl] - ethyl] - 2 - oxazolidinone and salts thereof, wherein there are used starting materials of formulae II and III, formula IV or formulae V and VI in which R_1

represents a methyl group, R_2, R_3, R_5 and R_6 each represent a hydrogen atom, R_4 represents a methylthio group, n stands for 2, m stands for zero and X represents an oxygen atom.

23. A process for the manufacture of the dibenzo[b,f]thiepin derivatives set forth in claim 1, substantially as hereinbefore described with reference to Examples 1 to 24.

24. Dibenzo[b,f]thiepin derivatives as set forth in claim 1, when manufactured by the process claimed in any one of claims 12 to 23 inclusive.

25. A pharmaceutical preparation containing a dibenzo[b,f]thiepin derivative as set forth in claim 1 in association with a compatible pharmaceutical carrier.

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